AFTERNOON SESSION

[1:15 p.m.]

CHAIRPERSON CANADY: At this time we reconvene the meeting. We are at the point in our agenda for really just open discussion in terms of general thoughts from the panel regarding the issues before us in terms of trial design. Does anyone want to be first in just general thoughts?

DR. ROSSEAU: I'll put out one question. Gail Rosseau from CINN Rush. It seems to me that there's a major issue here regarding what the endpoints are going to be for this and whether there is a radiographic or a clinically based endpoint. I'm interested in how the other panelists feel about that.

CHAIRPERSON CANADY: Just go and give your name.

DR. WALKER: I'm Cedric Walker and I'm a biomedical engineer, and since those of us who are biomedical engineers have not yet found a way to find French lessons in the brain through any known imaging modality, I would argue that there has to be a clinical endpoint, that the radiological endpoints are wonderful and they give quantitative data; but until the imaging endpoints are so good that we can, in fact, find the locus of the French lessons, we need to look at the patients foremost clinically.

CHAIRPERSON CANADY: Dr. Fessler?

DR. FESSLER: No.

CHAIRPERSON CANADY: Dr. Hurst?

DR. HURST: I would mention, however, that if we're looking at a device that's supposed to safely and effectively have an indicated use to reopen an artery, maybe that's what we should really focus on. And I think that eventually certainly the clinical outcomes are going to be of, very obviously, critical importance, that at least initially in most cases we've got to determine whether these devices do accomplish their intended use safely and effectively. And that, at least to my thoughts, would be: Do they open these arteries safely and effectively?

CHAIRPERSON CANADY: I guess my thought on that is it's interesting to me that throughout the conversation the EC-IC bypass is presented as a clear failed clinical modality and everyone agrees to that; but, in fact, angiographically the vessel's open. So that presents the obvious comparison in terms of whether that's an efficacious--whether it's an efficacious therapy as compared to whether it is technically possible and accomplishes. I think those are two different questions.

Yes?

DR. BECKER: I guess I would second the point that the clinical outcome is really the relevant outcome, although, you know, we have a lot of failed stroke trials.

And I'm thinking that a good surrogate secondary outcome might be useful such as MR lesion volume. We all know from the MS studies that MRI endpoints have proven to be efficiency, and I think that a therapy that does reduce lesion volume, while it may not change the clinical endpoint based on a gross Rankin Scale, may show that, yes, this therapy has some validity and over time we may be able to improve upon it. But I agree as a primary endpoint we really need to focus on the clinical aspect.

CHAIRPERSON CANADY: Yes?

DR. BROTT: With regard to the endpoints, I think it's essential to differentiate prevention trials from treatment trials, and the example cited of the EC-IC bypass trial I think is excellent with regard to prevention trials. And certainly in prevention trials the correlation of anatomy to clinical outcome has not been very close.

With our acute trials, though, things are fundamentally different in that before a stroke occurs, we know the vessels are open, and after the stroke occurs, we identify our occlusions. So we know that they're there, and there is very close correlation with the anatomy to the clinical deficit.

The clinical seems to work very well, as was demonstrated by several of our speakers today, when assessments and treatments are delivered very early. But as

things go by, the correlation gets a little bit more difficult, and from a clinical point of view, it is true that we could lower sample size if we looked at anatomy as well as clinical endpoints.

If a device is designed to open up an M1 occlusion and it does so, and it does so safely, there may be negative consequences with regard to reperfusion or reocclusion. But we don't understand that that's a serious problem at this point.

So I think that maybe the panel should consider for the acute treatment trials some way of trying to combine the clinical, which we all agree with, with a fundamental or a primary emphasis as well, really two endpoints, with regard to recanalization. All of us recognize the limitations of our drugs, and we want to help the development of treatments for stroke. And I think that will require recanalization, and I think that that needs to be very closely looked at, that approach to two criteria for success.

And I would just like to add in terms of MR imaging--and Dr. Grotta or Dr. Marler may wish to comment on this--that imaging lesions in stroke are so skewed with regard to volume distribution that they really require larger sample sizes. With the data that we have available today, they require larger sample sizes than even the

Barthel Index, which is probably, of the three general ways of looking at stroke clinical endpoints, the worst one. You know, the lesion size today I'm not sure is going to bail us out.

CHAIRPERSON CANADY: Other general comments? Yes?

DR. GROTTA: Just to add to what was just said about the recanalization, I think that the recanalization correlation is very time-linked in terms of outcome. If an artery recanalizes within the first few hours, I think there is good data that that correlates with clinical response; whereas, if the artery recanalizes six to 12 hours later, there's less of a correlation.

So I do have trouble with a long time window study that uses recanalization as an outcome, but if there's a study being done with early therapy, then I think recanalization could be evaluated as a secondary outcome measure. And I definitely think it could be used as a Phase II outcome measure to determine whether a recanalization strategy is effective at opening an artery up prior to designing a Phase III efficacy trial.

CHAIRPERSON CANADY: Dr. Marler?

DR. MARLER: To me, it's interesting to hear people advocating using surrogate outcomes, particularly imaging, with the implication that it's going to reduce the burden on the manufacturer for showing the effectiveness and

safety of a device, because the experience that I've had is that, despite spending millions of dollars looking at imaging outcomes as secondary or even primary outcomes in clinical research, the trials that use those have to be much larger, the sample size has to be larger, and it's much more difficult to randomize the patients in the long term. And the costs can be quite a bit higher, too, because of all the technology.

So I think there's very practical, down-to-earth reasons for looking at the clinical outcomes. I mean, the sample sizes are smaller. The effect is more readily interpreted--or translated to clinical practice; whereas the biomarkers for selection or outcome always end up being discussed and requiring additional research to confirm an initial result.

CHAIRPERSON CANADY: Other comments? Dr. Fessler?

DR. FESSLER: I have a comment, but I have a question first. John, I don't understand that. I don't understand how the n is going to be smaller in a clinical trial than it is in an outcome study that's just going to look at patency of the lumin.

DR. MARLER: I guess I'm talking about primarily the experience I've had with lesion size in stroke studies. And, actually, I'm not--other than the--I'm not sure that the even in PROACT II how that would work out as to what

would produce the sample size that was larger or smaller, whether it would be the recanalization or whether it would be the clinical outcome.

Jim?

DR. GROTTA: Of course, the PROACT II investigators--there are some here that can probably speak to this better than I can, but the difference between the recanalization rates in the treatment versus placebo group in PROACT II I believe was substantially bigger than the clinical effect that was seen. And I think that in our TCD experience, we see within the first two or three hours, even the first four hours, very good correlation between opening of the artery in major trunk middle cerebral artery occlusions and early clinical response. And, you know, that wasn't looked at in the tPA trial.

I agree with you 100 percent about the imaging infarct volume. In that situation, as you know--for those who may not know the study, looking at infarct volume differences required a larger sample size to see significance than looking at clinical differences in response to thrombolysis. But I do think that patency early on could be used as a measure of activity.

CHAIRPERSON CANADY: Other general comments?

DR. ZIVIN: I'd like to reemphasize that and make sure that it's clear. I believe that in Phase II testing,

imaging--looking at vessel patency is a perfectly sensible outcome measure for a Phase II trial. But I think that it is not an acceptable endpoint for a Phase III.

CHAIRPERSON CANADY: Dr. Fessler--

DR. KU: As someone who does a fair amount of imaging, I agree with the usefulness for a Phase II with respect to imaging. There's also been a lot of changes in imaging because, for many of the trials that have been done in the past, CT was used as a primary criteria for entry or non-entry into studies.

There's a lot of new types of imaging concerning brain injury versus relative perfusion of that potentially injured brain segment. And I think those are areas that need to be, you know, explored and better defined, and they may be very helpful in defining what patients are eligible for some of these studies versus which patients would potentially not benefit from some of these treatments.

CHAIRPERSON CANADY: Dr. Fessler?

DR. FESSLER: Just shifting topics somewhat a little bit, obviously the thing we've been talking about right now is appropriate selection of primary versus secondary endpoints. And the goal we're all trying to achieve is to decrease the length of time it takes to evaluate and approve a device while still maintaining a safe clinical environment.

The other issue that impacts upon that is appropriate selection of a control group. The argument's been made that at this point it's unethical to have certainly a non-treated control, but maybe even a traditionally treated control because the new therapies have been shown to be so much superior.

On the one hand, I really need to see further justification of that, and I tend to agree with you that after three hours traditional therapy is probably--is certainly not unethical and may be the best control group. But, on the other hand, I also want to encourage rapid development of new treatments and new devices.

I had the experience this last summer of going to a meeting in Europe--obviously, my specialty is spine--and was shocked to find that not only have we lost the leadership position in the United States in the world development of spinal devices and techniques, but we're six to seven years behind Japan and Europe, to the extent that I'm sending my fellows there for training rather than the United States. And we're doing that everywhere.

So my bias is to encourage more rapid development, but, on the other hand, we have to have reasonable arguments for clinical safety. So I would like the appropriate control group to be readdressed a little bit.

CHAIRPERSON CANADY: Ms. Wozner?

DR. WOZNER: I just want to add something, and Jim touched on this a little bit earlier; that is, when we're talking about recanalization, a lot of the discussion has really been limited to angiographic evidence, and I'd like to suggest that in centers where they've been able to demonstrate significant agreement between TCD findings and angiographic evidence that we also be able to include such non-invasive measures as evidence of recanalization.

CHAIRPERSON CANADY: Could just define TCD for everyone in the audience?

DR. WOZNER: Transcranial Doppler.

CHAIRPERSON CANADY: Any other general comments, or is the panel ready to move on to the specific questions?

DR. BROTT: I'd just like to respond that I think one of the important things to look at with recanalization would be reocclusion, and I think that transcranial Doppler might have a very useful role to play there when in a given patient you couldn't justify the risk of serial angiography but you could have TCD at the time of your, let's say, post-interventional angiogram and have a correlation, have a valid study, and then follow that patient, so that one can document, or not, ongoing durability of recanalization.

CHAIRPERSON CANADY: Other general comments? Yes, Dr. Becker?

DR. BECKER: I'd just like to make a comment about

the use of controls as well, and, you know, I think there's been good arguments put forth that we already know the natural outcome of certain stroke subtypes, but I would argue that, even based on a few things that were presented here, that is a moving target. And as we get better at stroke care, we know we need to treat glucose aggressively, and we've changed our treatment of blood pressure and stroke units are evolving. The natural history of those stroke patients is improving as well, and so I think you always do need to have a control group and can't use historical controls because the natural history is changing.

CHAIRPERSON CANADY: Other comments?

[No response.]

CHAIRPERSON CANADY: If we could then move to our discussion of specific questions, if we could ask Ms. Morris to return with the overlays.

I would remind our panel that the purpose this afternoon is really to get, to help define parameters for the FDA. It's not so much a right or wrong but to explore what we think are the appropriate rationales, to provide some guidance for them.

MS. MORRIS: Should I repeat the question, go through each one?

CHAIRPERSON CANADY: Yes, we might as well.

MS. MORRIS: Okay. The first question is:

Discuss what characteristics should be considered in defining the appropriate patient populations for each respective treatment modality. That means the preventive modalities as well as the treatment modalities. And there's three parts to that. The first part is: When considering inclusion and exclusion criteria in the design of the study, what specific criteria should be considered? And it gives some examples: symptomatic, non-symptomatic, primary and/or secondary treatment, the vascular region of the treatment, degree of collateral circulation, thrombus composition, and length of time after stroke for treatment. But if there are other issues you want to add, that would be wonderful.

CHAIRPERSON CANADY: I would suggest that we divide this conversation into the separate groups and take the acute first. Is that acceptable to the panel? So we're open, the floor's open to any questions or any comments regarding considerations for specific criteria for inclusion in the trial under the acute therapy group.

DR. HURST: I would mention that in the acute therapy, I think with a very short time window, we're somewhat limited in our ability to do sophisticated imaging evaluation so that we should probably focus more on CT or transcranial Doppler evaluation in that situation than some of the MR modalities.

MS. MORRIS: So you're addressing Question c?

DR. HURST: That's actually c.

MS. MORRIS: Right. Okay. In terms of Question a, is there--

CHAIRPERSON CANADY: We're talking about, I think, patient criteria for inclusion.

MS. MORRIS: Yeah, patient criteria.

CHAIRPERSON CANADY: In the acute trial.

MS. MORRIS: Yeah, would we be considering only symptomatic patients or would we be including non-symptomatic? If we're dealing with acute, I think that's a non-issue.

CHAIRPERSON CANADY: It's a non-issue. So symptomatic, any disease or patients specifically you feel should be excluded?

MS. MORRIS: Pre-existing illnesses?

DR. EDMUNDSON: In terms of acute CVA, in current trials, are occlusive diseases such as moyamoya amenable to stenting? That's more to the stroke guys here.

CHAIRPERSON CANADY: Could you repeat that? I didn't hear your question.

DR. EDMUNDSON: Individuals who have moyamoya disease have recurrent strokes and, of course, have significant stenosis usually in one of the MCA branches. Would a disease such as that be excluded from intervention in acute or preventive settings?

CHAIRPERSON CANADY: It seems to me one of the criteria that has been listed in some of the other studies, which would be an appropriate one here, would be that the stroke matches the distribution of the angiographic findings in terms of what we're treating and what we're trying to accomplish as a potential candidate in this category.

The moyamoya question I would think might become more complex. Do we wish to specifically exclude that? You certainly could have an acute occlusion of the middle cerebral in a patient who has an overall moyamoya syndrome.

What is the panel's thoughts on that?

DR. HURST: You know, that might fall under b, a particular cohort; whereas, just in general--I mean, we can talk about various cohorts, I mean, anterior and posterior circulation, M1 occlusions, more proximal occlusions, but I think there are definitely going to be cohorts and that's probably a good example of one of the separate ones.

CHAIRPERSON CANADY: So diffuse vasculopathy.

Any other thoughts about inclusion criteria in the acute group?

DR. KU: Yeah, with respect to the inclusion/exclusion criteria, if you're going to be treating acute stroke, it probably is pretty self-evident that you're only going to be treating symptomatic patients. Whether or not it should be a primary or a secondary treatment, I think

it could be either because there are many concomitant medical therapies that are going to be done at the same time.

Now, for vascular region of treatment, it depends on how complex or how simply you want your study to be. If you want to have a relatively simple study where there has been some historical correlation, you might want to design your study mainly for the anterior circulation. There's been obviously a lot of work done on other distributions, posterior circulation, but it seems like most of the current drug trials, most of the current thrombolytic therapy trials, either IV or intra-arterial, have been for the anterior circulation, at least the larger studies.

Now, the collateral circulation question is a real difficult one because--and it unfortunately may also be the most critical one with respect to this topic. It may even be more critical than the length of time after onset of the stroke. And the reason is because if you look at animal studies, if you occlude an end vessel in the brain, the brain is basically dead in five minutes if there is no collateral circulation. The reason a lot of studies show that there is viability of the brain in animal studies is because a lot of times the occlusions are more proximal, so there is collateral circulation.

So what you're really studying is you're studying

hypo-perfused brain or brain at risk for eventual death, not brain which is going to die right then and there.

So the other thing is the length of time after onset of stroke. Traditionally--and most studies have looked at a time window of anywhere between three to six hours, and that may be a very reasonable time period, because for the majority of patients, that's what has in the past been a reasonable time period where there is a statistically significant clinical difference. But that's looking at a broad population where it averages out to be between three to six hours.

If you're going to really analyze the concept of ischemic penumbra, then you may have to do types of studies where you have to do either a xenon CT or blood flow in order to determine what is truly at risk.

The reason many of the studies are not doing that is because they are relatively time-intensive and complex studies, and we're dealing with a problem where time is almost as important as getting that information. So that's where the real clinical dilemma comes in into designing these studies.

CHAIRPERSON CANADY: Any other thoughts on timing issues relative to inclusion criteria? Yes?

DR. MARLER: Yes, I think that there's a real opportunity here to change a direction and a pattern of

behavior, a pattern of continuing to repeat our failures. I think that if you look at the neuropharmacology, the neuroprotective approaches that have been taken, they've consistently looked at times that were far beyond what in the laboratory was shown to be a reasonable time to expect drugs to have an effect. And, ironically, some of the criticism has been that the laboratory models didn't work. But if you look at it carefully, the laboratory models very accurately predicted the totally negative results that have resulted from stretching the time window from two hours and occasionally three hours seen in the laboratory out to six hours.

I'd just encourage people in the devices arena to think about whether they really want to go to all the trouble to place the burden on the manufacturer of repeating their errors, the errors that have occurred in the pharmaceutical manufacturers, just by hoping that there is a benefit there without any real evidence. And I would strongly encourage people to think about how much easier it is as far as numbers of treatment to treat a smaller number of patients where you can see a larger effect because that's where the intervention can have the most easily demonstrated effect.

So whereas there may be a maximum time where you could possibly see a small benefit, it may be much less of a

burden on the people doing the trials and paying for the trials if they could get a much smaller sample size in a group of patients treated earlier where the effect that you're measuring could be a lot larger and start there and then maybe later try to expand based on some success rather than facing, as was done in neuroprotectants, one failure after another.

CHAIRPERSON CANADY: Other questions regarding timing, or thoughts?

[No response.]

CHAIRPERSON CANADY: Let me kind of summarize what I see that we have so far, and see what other thoughts people have.

Obviously, in the acute group, our sense is that the patient should be symptomatic, that there could be a primary or secondary treatment, that the timing, we're favoring a three-hour time zone, although there's some sentiment for a six-hour time zone.

I'm going to slip into the other questions because I don't think there's that much--the two groups that we would think of cohorting offhand would be moyamoya and the anterior and posterior circulation, and then an imaging in acute cases, CT scan with angiography.

Yes?

DR. EDMUNDSON: Comments about timing and imaging.

Since a lot of patients are occluded because by the time they get to an acute care hospital, it's well beyond three hours, and with diffusion, perfusion, imaging now, we can discern potentially viable penumbra. It may be worthwhile to have some strategy for a subpopulation of folks who, on MR imaging, as one of the imaging requirements, that may be a subset of patients who could have intervention beyond six hours.

CHAIRPERSON CANADY: So you might put those in the cohort group as another cohort?

DR. EDMUNDSON: Right.

CHAIRPERSON CANADY: Right. Yes?

DR. FESSLER: The concept that the difference between the perfusion and diffusion image is indicative of penumbra is not proven. It's a concept that a lot of people have been interested in for a few years now, and there's some testing going on to see whether that's true, but it is far from established, and I don't believe that at this point it should be used as an endpoint aside from use, again, in a research setting and not necessarily for an approval process.

CHAIRPERSON CANADY: Yes?

DR. BROTT: I would agree with that last comment. There now are a series of patients whose diffusion-weighted imaging defect has been totally reversed, and so not only is

it not proven, I think there is evidence that it's not reliable.

CHAIRPERSON CANADY: Other comments?

DR. GROTTA: I would second that, but I also would like to bring up another issue I'm surprised the endovascular folks haven't raised, and that is that one of the reasons why PROACT was probably successful is they addressed a specific location and type of stroke, namely, main trunk middle cerebral artery occlusions. And I think that the location and extent of the clot is very important in determining whether you're going to be able to lise the clot endoarterially. And I think that that's--one of the things asked in here was whether the thrombus location and composition and whatever, I think that certainly is something that should be standardized and targeted in a trial. Clearly patients with carotid occlusions are going to respond differently to--that's not to say that we shouldn't attempt to study those patients, but they're not going to be as easy to lise in somebody with a middle cerebral artery branch occlusion.

CHAIRPERSON CANADY: Other comments regarding--yes?

DR. BROTT: In that regard, those of you who read the House (?) , you can't have a fever if you don't take the temperature. And, of course, in PROACT II they've

restricted their study, their inquiry, to M1 and M2 occlusions.

For the interest of the panel, there is a new paper out which is just out this month in Stroke, and it's really, I think, very interesting and relates to that question very specifically. First of all, they did 20 patients with IV-tPA, which was initiated at a median of two hours and two minutes from symptoms onset, and then followed it--this was 0.6 milligrams per kilogram, and then followed it at a median of three hours and 30 minutes with intra-arterial tPA.

The reason I mention it with regard to Dr. Grotta's comments is they had six cervical ICA occlusions, four carotid terminus occlusions, eight proximal M1 segment occlusions, one M2 segment occlusion, and one severe carotid origin stenosis. And I'd invite all of us to take a look at this because one could not really predict the response based on the anatomy. So, clearly, we still have a lot to learn, and I think at this stage restricting to M1 and M2 may not be the best route.

The second point relates to what Dr. Marler mentioned. There's a very nice graph here. I'm sure you probably can't see it, but the bar graph refers to clinical outcome, and the higher the bar, the better the clinical outcome. And time, I'll just read, if you can see this,

time goes from 3.3, 4.2, 5.3, and greater than 6 medians. And you can see the pattern, to outline what Dr. Marler said.

Of course, the correspondence to a higher rate of response is the need for a smaller sample size.

DR. KU: I'd like, also on the imaging, to raise one point of caution. There has been raised the fact that there have been false negatives as far as diffusion imaging, but the thing is that if you look at the great majority of cases where there is a large diffusion deficit, the majority of time there will be a permanent deficit. So even though there are a limited number of false negatives, that's actually a small minority. So you have to be very careful not to throw out that modality because there's a small percentage of false negatives.

CHAIRPERSON CANADY: Dr. Becker?

DR. BECKER: With regards to timing, I think it's important to address the issue of IV-tPA. We're talking about restricting the time window for these therapeutic devices to three to six hours. Obviously, a large portion of those patients in the three-hour time window would be eligible for IV-tPA. And so how do you deal with those patients? Is it going to be a randomized trial between IV-tPA and the device? Are you only going to take patients who are not eligible for IV-tPA for some other reason and look

at best medical treatment apart from tPA and the device?

I guess that brings up the idea of cohorts as well, the tPA versus device versus best medical treatment other than tPA versus device.

CHAIRPERSON CANADY: Other thoughts? My sense earlier was that the committee felt--the panel, rather, felt that it was useful as both the primary and secondary, which my sense was would not exclude IV-tPA. Is that an accurate sense or not?

DR. GROTTA: Now you're getting into the appropriate control group, which is a separate question. But if you want to address that, I--

CHAIRPERSON CANADY: No, not yet to control. Selection still. Because the question was whether you would exclude all patients who had had IV-tPA.

DR. GROTTA: Well, if you're going to exclude them, then your control group becomes a placebo control group.

CHAIRPERSON CANADY: Right. Well, I think the feeling of the panel is not to exclude it.

DR. GROTTA: Right.

CHAIRPERSON CANADY: Is that a fair assessment?

Any other comments regarding acute treatment and these questions?

MS. MORRIS: Go to the second?

CHAIRPERSON CANADY: I was going to go--we have the preventive group as well.

MS. MORRIS: You're right. Sorry.

DR. KU: One comment. I guess I thought you were going to do 1 a, b, and c separately, but--

CHAIRPERSON CANADY: Well, we started--

DR. KU: --on the specific groups that may require assessment on their own data set, there was one other group that I was concerned about. Very often if you are going to do either a lytic therapy or other therapeutic treatment where you open up a blood vessel that was occluded or stenosed, it would be very important to put a subpopulation in that. There are certain patients where you do thrombolytic therapy and you find a fixed stenosis after the initial clot disruption or removal versus the population where you have patients with a blood vessel that's widely open, because very often those patients who have a fixed stenosis after you've opened them up, you may have to do a second intervention or treatment to prevent the thing from reclosing.

CHAIRPERSON CANADY: So you would suggest that we add as one of the criteria cohort evaluation?

DR. KU: Well, that's something to consider because you're looking at two different populations.

CHAIRPERSON CANADY: Yes, it makes sense.

Other comments?

[No response.]

CHAIRPERSON CANADY: Perhaps the little thornier preventative group relative to these same three questions. The first one would be inclusion and then cohort populations for the preventative and imaging techniques for the preventative group. Comments?

MS. MORRIS: Would it be simpler if we just say if there would be differences between the acute versus preventative?

CHAIRPERSON CANADY: Sure, yes.

MS. MORRIS: Does that need to be articulated?

CHAIRPERSON CANADY: Any comments from the panel regarding that?

DR. HURST: I think in the preventive group, you're going to have people who are at the moment asymptomatic, which, by definition, is not going to be the case in the acute group.

While there have been some very valid concerns brought up about including people who have failed best medical therapy, like the WASID group and things like that, that's really the group that you're going to wind up targeting, with those concerns in mind, because you're not going to treat someone with a new therapy who hasn't even had an opportunity to get the benefit of best medical

therapy that we have available now. So that's probably going to be at least one of the criteria that we need to look at.

CHAIRPERSON CANADY: So failed best medical?

DR. HURST: Yeah.

CHAIRPERSON CANADY: Other comments?

DR. BROTT: I would like to echo that, but generalize it a little bit more to symptomatic. We heard in our presentations today about the risk for stroke in asymptomatic populations with, let's say, stenosis of the middle cerebral artery, main stem, of greater than 50 percent. And the EC-IC bypass study in our folder I think points out the problem with using case series to estimate risk from fixed anatomical lesions. That was a big problem with the EC-IC because they estimated that the stroke rate would be much higher with intracranial asymptomatic disease--symptomatic disease. It wasn't even asymptomatic. You know, the rate of stroke with MCA occlusion--with high-grade MCA stenosis was only 5 percent per year, and I agreed with the statement that was made by Dr. Loftus on behalf of the AANS and the Cerebrovascular Section that at this stage, until we learn more, I really think that the studies should be restricted to symptomatic patients.

DR. GROTTA: But there's a difference between patients who are symptomatic--and I agree--and those who

have failed best medical therapy. And I think you can randomize patients who are symptomatic to an endovascular approach plus best medical therapy versus best medical therapy. I think if you wait for patients to fail warfarin therapy, as is pointed out, number one, it's going to limit the numbers of patients who you're going to put in your trial who might benefit. And there's no logical reason in my mind to think that a patient is more likely to benefit if they failed medical therapy than if they haven't. It's really more of an ethical issue. And I don't really see an ethical issue with randomizing patients before they've failed best medical therapy, as long as they've been symptomatic.

CHAIRPERSON CANADY: Could you define--

DR. BROTT: I certainly agree with that. I wasn't trying to take a counter position. I meant symptomatic patients, not those--not just those who had failed.

DR. MARLER: The reason I would argue for including symptomatic patients is probably based more on the generalization that you want to balance the risk of the new intervention versus the risk faced by the patient. And I think Dr. Grotta was pointing out a situation where it was a little bit different. So maybe it would be easier to say to balance the risk of the intervention to the immediate risk of the patient.

CHAIRPERSON CANADY: I'm confused. So maybe we can say--when Dr. Grotta was talking about a failed best medical, what is the criteria of--

DR. MARLER: Those patients are at a higher--

DR. GROTTA: Well, there was a statement made earlier that before--let's say someone with a middle cerebral artery stenosis, before they would be randomized in a trial, would it be necessary for them to continue to have symptoms while on warfarin therapy, for instance, or a combination antiplatelet therapy--

CHAIRPERSON CANADY: Okay.

DR. GROTTA: --as opposed to somebody who comes in who has had a stroke or a TIA, has a middle cerebral artery stenosis, they are symptomatic but they may not have already been on medical therapy other than maybe antihypertensive therapy. They may not have already specifically been on either antiplatelet therapy or anticoagulants. I think that person could be randomized to what we perceived as the best medical therapy plus stenting or angioplasty versus best medical therapy alone.

CHAIRPERSON CANADY: Okay. So the general--is it fair to say from the panel's perspective that we really feel that patients ought to be symptomatic in order to be treated and, therefore, we really don't have a preventative arm in the absolute sense of that word? Yes?

DR. FESSLER: I'll play devil's advocate here.

CHAIRPERSON CANADY: Okay.

DR. FESSLER: There is reasonably good evidence that asymptomatic patients with high-grade stenosis, that is, 90 percent or better, still have a very good--a better outcome with carotid endarterectomy than with medical management, would it not make sense to, on the basis of that, include that group in this study as well, that is, asymptomatic high-grade stenosis, rather than put ourselves in the position of approving a device for symptomatic patients only and having to repeat the entire process and take five more years to get that high-risk group of patients approved?

CHAIRPERSON CANADY: Comments?

DR. GROTTA: Well, that's what--I was attempting to support that possibility, that it might require the evidence of a very low risk, at least some preliminary evidence suggesting a very low risk of the intervention. I don't know if other people would agree.

DR. BROTT: I thought we were addressing intracranial disease. Extracranial carotid disease I almost think is a different topic.

CHAIRPERSON CANADY: Other comments?

[No response.]

CHAIRPERSON CANADY: My sense is we can move on to

Question 2. Does anybody object?

MS. MORRIS: Could I just clarify? In terms of the territory, would there be any differences in the region in which would be treated with a preventive therapy versus the acute?

CHAIRPERSON CANADY: We really have moved almost everybody into the acute therapy or failed best medical.

MS. MORRIS: Right. But the region in which you're going to give endovascular treatment, are you going to restrict it to any--certain vessels or--

CHAIRPERSON CANADY: In terms of intracranial vessels?

MS. MORRIS: Yes.

CHAIRPERSON CANADY: My sense was there wasn't a sense of restriction, but intracranial not extracranial.

MS. MORRIS: Correct. Okay.

CHAIRPERSON CANADY: For the purposes of our conversation today, at least.

MS. MORRIS: Question 2 is: Discuss what characteristics should be considered in defining the appropriate control population for a respective treatment modality.

CHAIRPERSON CANADY: Who would like to open the conversation?

DR. GROTTA: Well, that's already basically been

brought up, because I think if we're going to treat patients within three hours--we're talking about acute therapy now, going back to acute therapy. If we're going to treat patients within three hours, then I think patients treated with tPA have to be the appropriate control group. After three hours, then you can have a non-tPA-treated--I see, intravenous tPA, incidentally, beyond three hours you could have an intravenous tPA control--I mean, a placebo control group, although I guess one could raise the question of whether there--if you're talking about intra-arterial therapy, then I guess you'd have to have a non-tPA control after three hours.

T4B DR. BECKER: I'd say there should be no truly placebo-treated group. They should at least get aspirin. We should make that clear.

DR. MARLER: Couldn't you have--couldn't tPA in a way be considered part of a best medical therapy option and perhaps one advantage of the intervention would be--the other intervention would be that more patients would be eligible? Or I guess--in other words--I don't want to make it unnecessarily complicated, but someone ineligible for tPA less than three hours.

DR. GROTTA: Right. I mean, if you had a three-hour time window, you'd have to--again it would be your intervention plus best medical therapy against best medical

therapy, which in some cases would be tPA, and in those who didn't qualify, would not be.

DR. MARLER: I may be only talking about 5 or 20 percent of patients, but there are patients that you exclude from tPA, such as those on anticoagulants or with a history of hemorrhage that may not be a necessary exclusion for patients with endovascular--

DR. GROTTA: But the only thing is that there is--as was shown again in the trial that Dr. Brott alluded to, there may be additive effect of IV-tPA plus an intra-arterial approach, and those patients may respond much better because of the combined therapy. So I think you might want to stratify your data so that you could--and, again, this is something that probably goes beyond what we have to decide today, but it might make sense to look at those two groups in a way that you could separate out an effect between them. In other words, if your intervention may only be effective in patients who also get IV-tPA--or it may be dangerous in such patients and not in others.

CHAIRPERSON CANADY: Other comments?

[No response.]

CHAIRPERSON CANADY: So, in general, the feeling is best medical, which could include IV-tPA. Is that accurate? Yes, Dr. Fessler?

DR. FESSLER: It also needs to be defined more

specifically than that because if we're talking best medical, including tPA within three hours, that can be randomized very nicely. If we're talking best medical after three hours, then we're talking absolutely not TPA and just aspirin or another antithrombotic agent. So I think we're really talking about two different groups of study patients.

CHAIRPERSON CANADY: Okay. So pre-three hours and post-three hours.

MS. MAHER: Is it possible that the post-three hours, a historical control may be appropriate and have it nonrandomized as opposed to pre-three hours?

CHAIRPERSON CANADY: The committee's feeling on the historical control for the second group, beyond three hours?

DR. BROTT: I think that that question in a way has two parts to it, depending on the endpoint. If it's a clinical endpoint, then our historical control information is pretty limited with regard to intra-arterial techniques. The control group in the PROACT study was only 59 patients.

And on the other side, from the anatomical recanalization point of view, we know, of course, that pre-stroke the incidence of MCA occlusion is very low, and there's good literature. So I think the historical controls one could argue have more validity for anatomical recanalization comparison and less validity for a clinical

comparison.

CHAIRPERSON CANADY: Other comments?

DR. KU: One other option, in addition to using historical controls, is you can also have different sample sizes between your control population and your test population, so that if you have a very small control population but it's statistically significant, you can be able to enroll more patients into the treatment population.

CHAIRPERSON CANADY: Dr. Fessler--

DR. MARLER: I think there needs to be--oh, go ahead.

DR. FESSLER: No, please, go ahead.

DR. MARLER: Historical controls look easy from one point of view, but, I mean, they are fraught with danger. I think one thing we've really learned in acute stroke management and treatment is that just something as simple as the baseline stroke scale average for a group has much more impact on the outcome than even tPA for most--and probably for other interventions. So that while you may gain some convenience and it may reduce the amount of work to do the trial or the total number of patients, you're also taking a certain amount of risk about whether your group that you randomized--or that you treat is going to actually match up in a way that you could expect with the historical controls.

CHAIRPERSON CANADY: If I could summarize, I think where we are, we're saying there's a split between the three-hour and above-three-hour group, below three hours, best medical, including IV-tPA; post-three hours, then we have to think about best medical in terms of aspirin and other antithrombolytics and the question of whether or not historical controls may be of value in that group. But I think they're split on that opinion-wise within the panel.

Yes?

DR. FESSLER: One more caveat I want to throw in, just to make it more confusing. If we're already got evidence that says within three hours tPA, in fact, is statistically superior to other best medical treatment, then it doesn't make sense to throw those two groups together. Or do we want a three-arm study: best medical treatment non-tPA, best medical treatment with tPA versus stenting?

CHAIRPERSON CANADY: I think you could make that argument.

MS. MORRIS: Would you explain that again?

DR. FESSLER: We've got statistical evidence that says tPA is better than best medical treatment without tPA within three hours. So if now we're creating another study and we're saying we're going to compare stenting to best medical treatment including tPA, those are two separate groups.

CHAIRPERSON CANADY: Well, actually, the way we're doing it now is just who should be included, not so much the analysis yet. So we're saying that IV-tPA would not exclude you from being in this study. And then I think as we discuss the other--the cohort question there would come up. So you're suggesting back in really one that under the cohort would be with or without IV-tPA as a separate analysis.

Dr. Grotta, did I see a hand? Did I see another hand?

[No response.]

CHAIRPERSON CANADY: Any other comments regarding Question 2?

[No response.]

CHAIRPERSON CANADY: We can move on to Question 3.

MS. MORRIS: We've answered both acute and preventative.

CHAIRPERSON CANADY: I think preventative is gone.

MS. MORRIS: Okay.

CHAIRPERSON CANADY: I believe.

MS. MORRIS: It's going faster than my brain can go.

CHAIRPERSON CANADY: Sorry.

MS. MORRIS: That's all right. Question 3 is broken up into three parts. Discuss what considerations

need to be incorporated when identifying appropriate outcome measures to establish safety and effectiveness. That is, what specific considerations are needed to establish safety? And what specific considerations are needed to establish effectiveness? And any secondary safety and effectiveness measures?

CHAIRPERSON CANADY: Open the discussion?

DR. HURST: I would say that the primary condition consideration needed to establish safety is does this device damage the vessel, because, otherwise, if we just look at simple intracranial hemorrhage, that's certainly got to be a secondary endpoint here, but--

PARTICIPANT: Can you speak into the microphone?

DR. HURST: I'm sorry. Certainly intracranial hemorrhage has to be a secondary endpoint, but we're talking in many cases about time that is going to determine whether or not there is an intracranial hemorrhage rather than the device. So that I think if we're evaluating a device under these circumstances, we need to see whether it safely accomplishes its purpose of opening the vessel without damaging the vessel and, most importantly, without rupturing the vessel.

CHAIRPERSON CANADY: Other comments?

DR. WALKER: One of the manufacturer's presentations this morning urged recanalization as an endpoint, and

certainly if the indication of the device is limited only to recanalization with no mention of possible neurological benefits from recanalization, then one could make the argument that an angiographic study of recanalization is an appropriate endpoint for a device that only promises to do recanalization.

But as soon as neurological benefits are claimed on the label or in the indication, then recanalization becomes a secondary endpoint, and the neurological outcome has to be the first endpoint.

So I guess the answer to this question is for what claimed outcome, and it depends.

CHAIRPERSON CANADY: Dr. Witten?

DR. WITTEN: I'll just comment that that's one of the things we're hoping that the panel will help us with. There's already been a lot of comment on this so far, which is, if we take a product to panel--I mean, down the road if we have data and we take a product to panel, that is, where the study looked at a surrogate measure, that is one of the questions we ask the panel then, which is what does that measure show. So what we're trying to do here is try to address it in advance.

DR. KU: Yeah, I would think that, you know, showing patient benefit would be the most important thing. In the Phase II trials, you can use imaging criteria, et

cetera, et cetera, as far as vessel patency and things like that. But I think the bottom line is still patient outcome.

CHAIRPERSON CANADY: Dr. Fessler?

DR. FESSLER: Are we talking about effectiveness or are we talking about safety? It seems to me this entire discussion is really about b, not a.

CHAIRPERSON CANADY: Well, what happens is we started out trying to do them separately, and the conversation always bleeds over.

[Laughter.]

CHAIRPERSON CANADY: So I've conceded to the reality and you can discuss any of the sub-points you might wish.

[Laughter.]

DR. FESSLER: This is one area where we, in fact, can be specific because safety and efficacy are very different.

CHAIRPERSON CANADY: All right.

DR. FESSLER: Safety is very simple. I mean, it's death, stroke, perforation, and infection, as four primary endpoints for safety.

CHAIRPERSON CANADY: I would add to that, as I think Dr. Ku pointed out earlier, you know, stenosis at the site or injury to the vessel has to be considered as well.

DR. FESSLER: Perforation.

CHAIRPERSON CANADY: Right. Well, short of perforation.

Other comments on safety? Dr. Fessler sped us right through that one. Yes, Dr. Marler?

DR. MARLER: Where would one put reocclusion?

CHAIRPERSON CANADY: On the list.

[Laughter.]

CHAIRPERSON CANADY: Actually, probably under efficacy. Under b, the endpoint conversation, which is obviously a major issue here.

DR. MARLER: I mean, I think you've really got to look at both endpoints. If you try to look at clinical endpoints with the exclusion of the recanalization, you're going to find yourself in the position of an uncollateralized segment of vasculature reopened after maybe three hours that does very badly with a collateralized segment that may be effectively reopened after five or six hours that does very well.

The point that I'm trying to make is that as soon as you throw clinical outcome in there, the multitude of variables that you must measure expands exponentially, and we've run into that in the evaluation of some other devices. I think that certainly the clinical outcome is absolutely important, and it must be ultimately addressed. When we start talking about treatment for stroke, when we have

recanalization, we have neuroprotection, we have time factors, we have different anatomic factors in there, the practicality of it is that we need some very effective measurements that we can look at and really measure, and that's why I would lean towards emphasizing reopening.

DR. BROTT: I would like to second that. I think that at this point, if we restrict our primary endpoint just to clinical, we may have devices that today, with today's logistics, we achieve very good recanalization, but it takes, for example, a little bit too long, and it's six hours, and the primary endpoint is unsuccessful for a device that actually does a great job and is safe.

And I suspect that as we develop these devices over time and we develop our logistics and the time of delivery of the device begins to approach what Dr. Zivin showed us on the curve, that then we will have enough correlation between the clinical and the angiographic so that we may only have then to depend on one, the clinical. But I think to just--and that's why I like the idea of two primary endpoints for devices.

With drugs, we don't have the anatomy. They didn't have the anatomy with tPA. They didn't know what the drug was doing, and we kind of in some ways still don't know what the drug is doing. But here we do have an anatomical assessment before and after and with, you know, differing

techniques further on down the line. So I really think that we could delay treatment of our patients if we stick at this stage to just a clinical primary endpoint.

CHAIRPERSON CANADY: So am I hearing a sense of the committee for a dual endpoint?

DR. FESSLER: I don't have a problem with the idea of looking at vessel reopening as an endpoint in a study, but I can't see how you can make that into a primary endpoint for which you're going to give people approval to use a device.

You know, we've been hearing forever, well, we've got to--it works but we can't quite prove it and we've got another one coming along right now. Show me the one that works now. If you're going to advertise it and tell physicians that this is an FDA-approved device, I can't think of any other way other than to say that it works to make patients better.

CHAIRPERSON CANADY: Dr. Wozner?

DR. WOZNER: The bottom line really is that if you're going to be able to establish a cause and effect relationship, which I think is the interest of any investigator moving this way, then you have to look at those two endpoints in concert.

CHAIRPERSON CANADY: Other comments?

DR. HURST: I would agree with that. We've seen

that, for example, with the n-butyl cyanoacrylate embolic device that 20 years down the road, when we began to focus on does this device safely and effectively occlude the artery, we were able to show that it was, in fact, effective.

The clinical evaluation really slowed the approval of that device that had been available for quite a long time. So it's really the time and reality that we have to look at there.

DR. BECKER: I would just say that it really then comes down to trial design. If you get a device that works very well and opens the vessel, you need to prove that it works by using it in the appropriate time frame. And that's what it all really comes down to.

DR. ZIVIN: Again, I guess I don't--maybe I'm missing something about the argument here, but it seems to me that nobody is arguing that you shouldn't use the vessel reopening as an important endpoint in proof of principle. But when you're talking about approving a device for use in patients for routine medical care, I don't see how you can use that as a primary endpoint.

CHAIRPERSON CANADY: Other comments? Yes?

DR. BROTT: It seems to me that nobody is arguing that recanalization should be the primary endpoint; rather, that one could argue that there should be dual endpoints,

and when those studies or that study is brought before the panel, it's the responsibility of the panel to weigh the relative benefits of the device, its safety and its efficacy based on those two dual endpoints.

CHAIRPERSON CANADY: Sally?

MS. MAHER: I would also just remind everybody that when we're looking at this--and I would agree with everything that's just been said, but when the devices actually come to the panel, we're doing a balancing act of risk versus benefit and the information that we've collected from the clinical trial. So the whole picture will have to be looked at.

CHAIRPERSON CANADY: Other comments?

DR. EDMUNDSON: Yes, in thinking of study design and cost, if you're going to look at dual endpoints, then, of course, if they're on best medical arm versus the device arm, of course, everyone at baseline will need angiography, what do you do with dual endpoints? The medical arm, repeat angio? Otherwise, you're dealing with different risk rates.

CHAIRPERSON CANADY: Other comments?

DR. MARLER: I think clinical outcomes are exceedingly important. The other outcomes can be important as well, but I don't know of anything that out-trumps clinical outcome.

DR. FESSLER: I can create a scenario that would

make it very confusing. We'll take a group of patients and we'll stent them and we'll give them, in addition, best medical care. And due to some statistically aberrant selection of our patients, this group really does great, but none of their stents were open. So here we have two endpoints, one clinical, one mechanical, opening of their vessel, where they clinically got better but their vessel didn't open.

So I don't see, if we're going to be putting in a stent to revascularize, I don't think we can not have as a primary endpoint revascularization. But I also don't think it can be the only primary endpoint. I agree we have to have two.

CHAIRPERSON CANADY: Dr. Witten?

DR. WITTEN: Yes, I'd like to just add on a question to this while we're on Question 3 about endpoints. And just setting aside for the moment the question about what's a primary endpoint, what's a secondary endpoint, whether it's safety or effectiveness, I wonder whether we could get some input from the panel on how you would actually measure angiographic success, both for the acute and the prevention group, that is to say, you know, you do an angiography, what number--how do you arrive at a number or a description that would tell you whether or not you have successfully recanalized? For both--perhaps we could

discuss both of those, acute and prevention.

MS. MORRIS: Like to what degree of recanalization would be considered a success?

CHAIRPERSON CANADY: Do any of our radiology colleagues--

DR. WITTEN: And how you measure.

MS. MORRIS: And how you measure.

CHAIRPERSON CANADY: Go ahead.

DR. GROTTA: Well, those have already been established for coronary perfusion, and they've been adapted to cerebrovascular trials. And there have even been correlations with ultrasound and such recanalization, partial or complete TIMI flows. I don't see any reason why that shouldn't be used, at least for the acute trials.

As far as the reocclusion trials, you know, you want to know whether there's residual stenosis, and then, of course, look at the occlusion or restenosis down the line.

CHAIRPERSON CANADY: Other comments?

DR. FESSLER: I have two questions regarding that. Number one, since we're talking about a vessel now that is 1 millimeter rather than 6 or 7 millimeters, is angiographic technique sufficient to say we've got a 50 percent increase in diameter of the vessel; and, number two, is there a difference in the characteristics of the ultrasound feedback we get after we stent an artery if we're doing an ultrasound

image through the stent. So is that accurate as well?

DR. HURST: I would say we're really looking at larger vessels than a millimeter. We're probably looking at vessels in the range of 3 millimeters or larger in order to make those measurements effectively.

MS. MORRIS: So that would get back to territory again. If you are going to use those measures and you are going to use radiographic measures as an additional primary endpoint, then wouldn't it be--the vessel region you choose to apply therapy would be limited based on the limitations of--

DR. HURST: It would certainly have to be big enough to do the measurements, and I think that most of the cohorts at least that I was sort of visualizing would be large vessel occlusive strokes. If we're talking about lacunar disease or a disease that may be too small to visualize angiographically, then I think we're into a whole other ball game.

CHAIRPERSON CANADY: Other comments?

[No response.]

CHAIRPERSON CANADY: The final portion, other secondary safety and effectiveness measures that we would want to assess? Restenosis certainly might come in that group.

DR. GROTTA: I think for the prevention issues,

cost and patient acceptability are one of the major attractions of endovascular approaches as opposed to surgery. So if you can show that the outcomes are the same but the hospital costs and patient costs and quality of life and things like that, even though we don't know how to measure--maybe we don't know how to measure all of those quite so well, but I'd say that it would be incumbent upon us to do it because that's one of the things that drives patients to want to have endovascular approaches.

CHAIRPERSON CANADY: One thing I was just noticing as I was looking back at my notes that we didn't include that all of the speakers largely included was just the issue of wounds and complications of the angiography itself. And I don't think there's any disagreement in the panel. I just wanted to state that for the record. So cost, quality of life inputs, safety and effectiveness. Anything else the panel would like to...

[No response.]

CHAIRPERSON CANADY: Any general thoughts about this portion before we close this portion of the conversation that anyone would like to add, any panelists?

[No response.]

CHAIRPERSON CANADY: Dr. Witten, would you like further direction?

DR. WITTEN: No. Thank you.

CHAIRPERSON CANADY: Does that answer that?

MS. MORRIS: Question 4: What sources of bias and confounding factors should be considered in the design of these studies? And the two parts are: How should combination therapies be considered with respect to trial design? And how should concomitant medication be considered in the trial design?

CHAIRPERSON CANADY: This I think goes back to Dr. Fessler's question of analysis.

DR. GROTTA: I think this is the hardest part of a device trial because, you know, there are so many different associated things that go on. What about stenting, residual stenoses? What about the use of GP2, BA3 antagonist? Dose of heparin clearly is related to results in the PROACT trial. What about using an intra-arterial approach to amplify the effects of neuroprotective drugs by delivering them to the bed of the infarct better?

So there are all sorts of questions that could be asked here and different permutations. I think it's going to be very difficult to answer this question other than to recognize the potential for confounding variables to occur and for these things that need to be addressed in any trial design.

CHAIRPERSON CANADY: Yes, Gail?

DR. ROSSEAU: I think this will be one type of

trial in particular where informed consent issues could be extremely thorny because we have a situation where we will probably have many of the investigators are also partial owners or in some way paid by the companies whose products they are using in an investigational way. And that needs to be known, in my view, by the patient before they sign informed consent, and that is not always the case.

CHAIRPERSON CANADY: Other comments?

DR. KU: One suggestion would also be, because of the proliferation of drugs or devices that are being used in non-approved ways is that if you're going to do a trial, that you pretty much stick with, you know, conventional, approved types of treatments if you're going to do multiple therapies, medical plus endovascular.

CHAIRPERSON CANADY: So that the best medical, best surgical, would include approved label?

DR. KU: Should be approved labeling. Otherwise, you're going to make it really difficult.

But then that also--you know, the question is: Do you want to do a two-arm study or do you want to do a three-arm study? If you want to do a three-arm study, then you might consider doing non-approved uses of the other medications or devices?

CHAIRPERSON CANADY: Comments?

DR. GROTTA: Heparin is not approved--has not been

proven effective in acute stroke, yet it was used along with Prourokinase in the PROACT trial. And we're hearing that most centers that are doing stenting of extracranial vessels, and intracranial vessels, couple it not only with antiplatelet drugs but also heparin and GP2, BA3 antagonist. So, I mean, I think that it would be difficult to do a trial without factoring in those additional drugs, and I think this is an evolving science or art, whichever way you want to call it, and probably whatever we say now is not going to be the case six months from now or a year from now whenever such a study comes before you. I just think we have to recognize that there's a tremendous potential for confounding variables in such a study, and they have to be addressed in the trial design.

CHAIRPERSON CANADY: Other comments?

[No response.]

MS. MORRIS: Okay. So you'll leave it our lap, huh?

[Laughter.]

CHAIRPERSON CANADY: We've given you much latitude.

I believe this concludes this portion--

MS. MORRIS: Question 5.

CHAIRPERSON CANADY: One more question. I'm sorry.

MS. MORRIS: Yeah, one more question. Question 5 deals with: When should evaluation of these outcome measures be made, for the primary and secondary effectiveness measure? And what should be the length of follow-up to establish their safety for the therapies?

CHAIRPERSON CANADY: Open for comment.

To some extent, a primary is a clinical and radiographic primary.

DR. HURST: You know, with the acute, the primary could probably be done immediately if we're looking at angiographic endpoints. In terms of clinical endpoints, certainly you'd want a clinical endpoint within 24 hours as soon as you get out from the acute effects, because many of these are done under general anesthesia. You don't want to try to compare that with a pre-anesthesia exam, so maybe at 24 hours before the initial endpoint.

CHAIRPERSON CANADY: Other comments?

DR. BROTT: I would agree with the comment that Dr. Zivin made earlier that the three-month outcome that has become somewhat traditional is definitely arbitrary. And I think that there is evidence now that that time could be pushed closer to the time of the clinical event. How close? The NINDS tPA trial is very interesting, another paper just recently on the combined endpoints. The patient status at 24 hours actually was a quite good predictor in terms of

outcome in three months, and I'm not sure that we're ready to move from three months to 24 hours. But I think that, you know, strong consideration in terms of trial design should be given to earlier assessment.

DR. GROTTA: I'd just like to add another point there. I think it depends on the treatment. If you're looking at intra-arterial recanalization where you're likely to see rapid dramatic response, then early outcome makes sense. But if you're talking about a different kind of therapy, like a neuroprotective therapy, where the results may be more subtle, the more prolonged outcome might be more relevant, but it also brings in another point that I didn't mention in the last question, which we now need--which needs to be added, and that is the influence of rehabilitation, because there's increasing evidence--and I think all the neurologists are aware of this--that various restorative therapies, including rehabilitation techniques, may--probably do have an impact on the speed and completeness of recovery, and that is another variable that's not usually controlled for in trials that probably needs to be considered in any trial, particularly if you're going to have a long outcome like three months.

CHAIRPERSON CANADY: Other comments?

DR. FESSLER: Have we totally eliminated the prevention aspect of this and are we just dealing with

acute?

CHAIRPERSON CANADY: The sense I had earlier was that people felt the patient should be symptomatic or failed medical, so the answer is yes.

DR. FESSLER: Okay. Then one of my comments is useless, more useless than the others.

[Laughter.]

DR. FESSLER: But the other thing regarding safety is probably not necessarily part of the primary study, but I think it's important to do a post-market analysis to see what's going to happen to these stents down the line. If, for example, over a two-year period these stents get stiff, for example, and you've got a stent going around a bend in an artery, then we could restenose just by kinking off at the end of the stent and we won't know that if we don't do a post-market analysis.

CHAIRPERSON CANADY: Dr. Witten?

DR. WITTEN: Yeah, actually, that related to my own question, which is the comment about assessing the success of the trial, the primary and secondary effectiveness related to the acute treatment. But I wondered if there are any additional comments relating to when we should do these assessments for the trials for prevention of recurrent events. And that's one comment that related to that, but if there are any others, we'd

appreciate hearing them, too.

CHAIRPERSON CANADY: Yes?

DR. WALKER: The burden of imposing a post-market analysis on biomaterials whose properties are known given the unlikely hypothesis that they might stiffen seems to put an awful lot on the manufacturers, and I'd urge the FDA to be very cautious about requiring that unless the material in some way could possibly allow for that possibility.

DR. BECKER: I guess I would make another call for--another reason for a call for post-marketing analysis. If we prove that stenting in the M1 artery improves outcome from acute stroke or whatever therapy you're talking about, and that's done--those trials are done in very academic centers where people have a lot of experience, and suddenly the devices become available and you have general radiologists in the community who are starting to do this--and we see this all the time, at least in my community--the outcomes are very different when you don't have experience. And Dr. Alberts presented a lot of that data today with regard to carotid stenting.

So I think you have to be careful. Obviously there's going to be a learning curve for some of these things, but I think looking at how these therapies are used in the community is an important thing to do.

DR. MARLER: I wanted to say on preventative

therapies, the length of follow-up can be too short, and that can work against--make it easier to reject a potentially successful device. I know that most of our NIH peer-reviewed prevention studies have an average follow-up, at least planned, of closer to three years than to one year. And the reason for this is there's usually a complication rate early on in the peri-operative or peri-procedure period, and it takes time to overcome that. And it depends on the basal risk of the recurrent event, and often that can only be 5 to 8 percent per year, which is often just a trade-off with the complication rate of some of the procedures. So it might be better to have a longer follow-up period so you have a better chance to see the overall benefit.

CHAIRPERSON CANADY: Other comments? Sally?

MS. MAHER: I just want to follow up a little bit on what Dr. Walker said about the cost of the post-market surveillance. I think we need to be very careful as a panel not to arbitrarily suggest that we're almost always going to need post-market surveillance but, rather, to look at it on a case-by-case basis as the devices come before the panel, because it's very expensive to the companies and may keep companies away from looking at different technologies.

CHAIRPERSON CANADY: Dr. Witten?

DR. WITTEN: I just want to ask again, I mean,

we've sort of jumped from acute stroke measured at a month to what kind of post-market surveillance for these prevention of recurrent events. And so I'm wondering if anybody--and, actually, Dr. Marler also commented on when the study should be assessed. I'm wondering if there's any other comments on when we should be assessing success of the study for a study design to prevent recurrent events.

DR. HURST: For the prevention ones, probably looking at longer term is going to be necessary. If you look at some of the endarterectomy studies, you're looking at two-year follow-ups, you're looking at five-year follow-ups. And when we talk about restenosis, we really can't expect to catch most of the restenosis if we stop follow-up at less than a year. So that we're probably looking at two years if we're really going to catch restenosis and expect to really evaluate prevention.

CHAIRPERSON CANADY: And effectiveness.

DR. HURST: Yes.

CHAIRPERSON CANADY: Other comments?

DR. BROTT: I think that could be modified a little bit to say that with Kaplan-Meyer techniques, one can validly come up with five-year rates if you have sufficient follow-up for two to three years in the great bulk of your patient population. And this, in fact, is what was done with NASCET and what was done with ACAS where the follow-up

was not five years. The average follow-up was much shorter, but with the Kaplan-Meyer techniques, adequate projections were possible.

DR. GROTTA: And remember, again--I may be wrong because I have not been on a device panel before, but if the objective is to--it's really a statistical question. If your objective is to show equivalency or certainly no worse than statistically, you probably wouldn't need as long a follow-up. You just want to be sure that things aren't worse with your device. So I think it's a statistical question based on your sample size how long you need to follow the patients to be sure that you have at least equivalency based on the number of events that are occurring in your control group.

CHAIRPERSON CANADY: Yes?

DR. ZIVIN: I think it's hard to come up with a hard answer to a question like that at this point. Some of the studies--I don't show the data--the curves separate instantly or very quickly thereafter and show no sign of coming back after a number of months, and under those circumstances I think that that ought to be approvable.

On the other hand, sometimes the curves separate only very slowly, and I think the manufacturers are actually going to be in a much better position to tell you what works ubest for their device.

So certainly the follow-up shouldn't be too short, but I don't think that you can put an outer limit on it.

CHAIRPERSON CANADY: Other comments?

[No response.]

CHAIRPERSON CANADY: Is there a Question 6?

MS. MORRIS: No.

CHAIRPERSON CANADY: All right. Any other general comments before I bring this portion of the panel meeting to a close?

[No response.]

CHAIRPERSON CANADY: We are going to bring this portion to a close. I would ask that people not wander far. I'm going to begin the second part quite promptly as soon as we allow people to leave the room. So let's plan to start again at quarter to 3:00.

[Recess.]

CHAIRPERSON CANADY: We're back on the record. We will begin with the FDA presentation of neurological protective cooling. Again, Ms. Janine Morris will introduce our second topic. Ms. Morris?

MS. MORRIS: Thank you. The first topic discussed earlier today was the use of medical devices in the intracranial circulation to directly treat an ischemic event associated with a blood clot and the use of medical devices to treat atherosclerosis of the intracranial arteries to

prevent an ischemic stroke.

This afternoon's topic focuses on devices designed to provide neuroprotection by systemic or localized cooling for several different indications.

Use of hypothermia as a neuroprotectant has been proposed for patients who have sustained a stroke, cardiac arrest, and severe head injury, as well as for patients undergoing intracranial surgical procedures such as cerebral aneurysm clipping.

There is a range of technologies that have been reported to provide hypothermia such as cooling blankets, cardiopulmonary bypass, external metal plates, cooling beds endovascular cooling catheters, and devices that provide selective cooling to the blood supply of the brain.

These methods can result in overall core body cooling or have focused effects limited to the brain only.

Literature reports date to 194 when the therapeutic use of hypothermia in a patient with blunt head injury was first reported. Subsequent reports include the role of hypothermia in preventing or reducing the effects of artificially created ischemic stroke damage in animal models.

These studies have induced hypothermia, body temperatures as low as 32 degrees, either at the time of stroke or at various times following the onset of stroke.

Other literature describes the potential value of cooling to provide neuroprotection, for example, in patients who have been resuscitated after cardiac arrest, patients with intracerebral hemorrhage, and patients with intracranial aneurysm rupture.

The purpose of this afternoon's discussion is to get the panel's recommendations on clinical trial considerations for medical devices intended for deliver neuroprotection.

We will ask two general questions about safety parameters to be measured and temperature monitoring recommendations. The remaining questions relate to study design issues for four specific patient populations, that is, cardiac arrest patients, traumatic head injury patients, stroke patients, and patients undergoing aneurysm surgery.

Therefore, to help facilitate the discussion, we have structured our questions to focus on the specific safety considerations associated with cooling and any unique trial design issues for those proposed indications, and then I have the three questions that I can review.

The first question is: What are the primary safety parameters that would be important to measure in any study population, in particular, any safety concerns related to target temperatures, duration of hypothermia, rate of cooling, and rate of re-warming? Also, are there safety

questions that are unique to specific technology either because of the technology or the procedures needed to implement the technology?

The second general question is: What are your recommendations for temperature monitoring methods and anatomic sites?

What are your suggestions for clinical study design in evaluating hypothermia devices in the following patient populations? And there are four patient populations. Many of the questions are similar for each population, but there are some differences so I'll go through each of them.

Cardiac arrest patients: What are important inclusion/exclusion criteria to be considered in this patient population? What safety parameters are important to be measured? What considerations should be taken into account when identifying appropriate outcome measures? When should primary and secondary effectiveness outcomes be measured? And what characteristics should be considered in defining the appropriate control population?

For traumatic head injury, again, what are the important inclusion/exclusion criteria? What are the safety parameters? What considerations should be taken into account when identifying appropriate outcome measures? When should primary and secondary effectiveness outcomes be

measured? And what characteristics should be considered in defining an appropriate control population? And are there special considerations that should be taken into account when treating pediatric patients?

The third part: We have already heard many helpful comments from the panel regarding--with respect to acute ischemic stroke; therefore, any information related to 3c that we've discussed earlier don't need to be reiterated here. But the subparts for stroke population would be: What important inclusion/exclusion criteria should be considered? What are the safety parameters? What considerations should be taken into account when identifying an appropriate outcome measure? When should primary and secondary effectiveness be measured? And what characteristics should be considered in defining the appropriate control population?

Then, finally, although we believe that clinical benefit of hypothermia needs to be assessed for patient populations identified in 3a through c, we recognize that in some centers hypothermia may already be a part of intraoperative management--we recognize in some centers hypothermia has already been a part of intraoperative management of patients with intracranial aneurysms who are undergoing surgery. Therefore, depending on the extent to which this is an accepted standard of care, it is our intent

that these questions for stroke may be highlighted-- highlight some differences in terms of the types of study endpoints and control treatments that may be used in a study of this specific patient population.

CHAIRPERSON CANADY: Thank you very much.

We're going to move now to the second open public hearing on the design of clinical trials for devices to provide neurologic protective cooling.

I would remind everyone addressing the panel of the need to speak into the microphone, and at this time I'd also like to remind the panelists, as the transcriptionists are having a little bit of difficulty when we get into conversation with ourselves instead of the microphone, that it's important for people who come to the microphone to give their name, whatever affiliations they may have, and also whatever financial interests they have.

We have three speakers known in advance. The first one is Dr. Loftus, who will be speaking for the AANS and the Congress of Neurologic Surgeons.

DR. LOFTUS: Thank you very much. I would like to speak once again about the ideas of the Joint Section AANS/CNS on clinical trials of cooling devices, and I'll try to educate a little bit and say a little information of what we're doing with the aneurysm trial that's currently underway.

I reiterate once again my strong philosophy that we get our best information regarding things that changed cerebrovascular surgery from Level 1 evidence trials. As I said this morning and I reiterate, in my mind for surgical considerations previous studies are obsolete when we have Level 1 evidence available to us.

There are a number of intraoperative protection strategies surgeons use. Pharmacologic, you are familiar with all of these; anesthetic. We want to talk about hypothermia today, which can be stratified into deep hypothermia, which is probably not the province of what we'll discuss here, and moderate or mild, which would appear to be fairly synonymous terms when one talks about hypothermia.

A little background. Deep hypothermia at the present time, this is Lawton's paper. Current indications for giant--these are cardiac arrest cases--giant complex aneurysms that cannot be treated conventionally or recur after placement of GDC coils. This is not what I seek to address today.

To show that mild hypothermia is in use, one of our other speakers, Dr. Ogilvy--this is Dr. Ogilvy's paper. This is really not to stratify out hypothermia, but just to say that this along in a core protocol--to show you that he used a protocol of a core temperature of 33 to 34 degrees

Centigrade, which is what we recommend here. So it is in use and published.

Potential uses of hypothermia, we've already heard to be discussed today. Cardiac arrest patients I will not discuss. It's really out of my area of expertise. Traumatic head injury patients, yes. Stroke patients, yes. Aneurysm surgery patients is what I really have the greatest experience with.

Why should we study hypothermia with randomized trials? Different reasons than we had this morning. Number one, hypothermia is being used empirically and, I would suggest to you, with very little evidence to speak to its efficacy. But it is--and I will tell you that when we recruited centers for the IHAST2 trial, the hypothermia aneurysm subarachnoid hemorrhage trial, NIH-funded, double-blinded, randomized trial, difficult to recruit some centers because they said we use hypothermia empirically, and we don't want to deny a treatment that we feel is beneficial to our patients. Obviously we have ethical differences with that.

No Level 1 evidence of efficacy. Potential risks exist, and I will show you that. Hypothermia is being studied for head injury and for stroke, and we're studying it for aneurysm surgery.

When we were in the process of designing the

IHAST2 trial--and I express my gratitude to John Marler for all his help in getting the IHAST2 trial funded and on the way--we queried the practice of aneurysm surgery in a number of centers. Protective strategies during aneurysm surgery used in 89 percent of the centers that we queried; 84 percent used occasional hypothermia. The target temperature customarily mild to moderate, 33 to 34 degrees, as we mentioned.

It's not without risk. What are the potential risks? Cardiac arrhythmia, coronary ischemia, infection or poor wound healing, and aggravation of cold-related diseases such as cryoglobulinemia, sickle cell anemia, or severe Raynaud's disease.

When hypothermia has been looked at for head injury, mild hypothermia, there is some evidence to suggest efficacy for GCS patients 5 to 7, a significant improvement in outcome at 3 to 6 months, and good outcomes appear to be greater in the hypothermic than in the normothermic group.

We will hear more today about how hypothermia can be delivered. There are several methods. Surface cooling--and I will admit to you that the industry representatives will know more than I about the methodology. Surface cooling passive is basically a failure to keep the patient warm. As you know, patients in surgery will cool passively just of their own accord. Active by surface cooling, now we

can--it can be cooling blankets. Now we use a polar air, chilled forced air refrigeration unit. That's what's used in the IHAST2 trial. Cooling of the inspired air is possible, and endovascular cooling, with either endovascular IV fluids, not as effective, or transvenous active blood cooling, which we will hear more about.

I point out to you clinical randomized trials are being done at the present time, so we're different than we were this morning. We are doing--and I will share with you the results of the IHAST2 trial, NIH-funded, randomized, blinded to the surgical investigator, with surface cooling. Unruptured aneurysms are being studies in, I believe, an industry-funded trial at Stanford with endovascular cooling technique. I am not directly familiar with this. And the stroke trial you'll hear more about in just a few minutes, the cool-aid(?) trial. The method of cooling is as yet under discussion.

Let me share with you briefly the ongoing status of the intraoperative hypothermia aneurysm, subarachnoid hemorrhage trial 2. I can't show--I don't have time to show you all the eligibility criteria, but basically what I want to show you are the things that we feel are failing points in our ability to cool patients. We cannot cool large patients effectively in the time frame that we want to with the body mass index of greater than 35 kilograms per square

meter. And, likewise, we will not cool patients who have contraindications to cooling, as I outlined to you previously, cold-aggravated diseases. And I think these are important things to keep in mind in the study designs that may come out this afternoon.

What do we do? We use refrigerated surface cooling. We take patients down to a target temperature of 33 degrees or leave them at 36.5 at the time a clip is applied, and then we immediately re-warm them with forced air re-warming with the idea to be normothermic when they leave the operating room or certainly in the recovery room.

In terms of follow-up with IHAST2, because, as I said this morning, when we were going to talk about acute therapy trials, there are both positive and negative benefits. So we are looking at immediate evaluations in the hospital, daily evaluations by a study coordinator, but the primary assessment, like in many of the stroke trials that we saw with surgery, with carotid endarterectomy, is an assessment at three months, which, as Dr. Zivin said also this morning, is fairly standard.

We have no data from the IHAST2 trial. If codes are not broken, the data is not unblinded. What does that mean? That we have not identified safety issues that would require unblinding; we have not identified a stopping point that would require unblinding. So the trial is ongoing with

patient entry. This is data from the pilot trial that was done in preparation for submission of the grant. No statistical difference between cool and regular, normothermic patients. But there were trends, only in subarachnoid hemorrhage patients, which is why the trial was narrowed down to subarachnoid hemorrhage: better brain relaxation, less post-operative ventilation, fewer NIH stroke score declines post-op, and better long-term function, i.e., improved Glasgow Outcome scores.

Future studies which will be discussed today, the technology is evolving. For example, the Polar Air unit--and this is what I meant this morning when I said stabilization of technology before we make final determinations about randomized trials. The Polar Air is off the market. We're using it for our trial. It's no longer being marketed. So other strategies will come along to cool patients intraoperatively. The question of brain temperature was very important to our deliberations. We do not do invasive monitoring of brain temperature. We use extrapolated data from core temperature, and it's felt that this was scientifically valid. But it certainly was a major question in our reverse-site visit and our entire review process.

Complications for trials you may design today can be extrapolated from IHAST2, and I will tell you that so far

there's no evidence of a safety issue either in the pilot trial--we did not identify a difference in any of these safety issues between the two groups or in IHAST2 itself; i.e., we haven't had to unblind the trial.

Adherence to target temperature protocol is crucial, and we are wrestling very seriously with this in IHAST2. Luckily, we've had very good results in adhering to it, but any failure, slight cooling, a slight cooling by passive methods in the normothermic group, we feel will invalidate the results.

That concludes my remarks. Thank you.

CHAIRPERSON CANADY: Thank you very much, Dr. Loftus.

Our next presentation is going to be done really as a tandem group, starting, I believe, with Dr. Krieger--no, starting with Dr. De Georgia. If you'll remember to identify yourself, affiliations, and financial interests, we'd appreciate it.

DR. LOFTUS: I apologize. I had no conflicts.

DR. DE GEORGIA: Good afternoon. My name is Michael De Georgia. I'm the head of the neurological intensive care program at the Cleveland Clinic Foundation, and I come here as a clinician, a neuro-intensivist, and a stroke specialist. I have no financial interest in hypothermia.

I'm here with my colleague, Dr. Krieger, also from the clinic, and we're going to share with you our experience in hypothermia, induced moderate hypothermia for acute ischemic stroke. In the first part of this talk, my part, I will review kind of the background of hypothermia and the rationale and the methodology that we used in this approach. In the second half, Dr. Krieger will go over the preliminary results which will also be presented at Fort Lauderdale in the Stroke Conference. We've called this pilot trial Cool AID, for cooling for acute ischemic brain damage.

As everybody knows, acute stroke is the third leading cause of death in the United States and the leading cause of disability. Thrombolytic therapy in general--IV-tPA and in selected cases intra-arterial thrombolysis--has improved outcome, but, really, the prognosis for patients with very severe strokes remains still pretty dismal.

Severe ischemic stroke leading to functional dependency constitutes about 10 to 15 percent of all acute stroke admissions, but as those of us who take care of these patients know, these are the patients who end up in the ICUs for sometimes weeks, and we often are able to pull them through this acute period only to have them discharged to the nursing home with a bad deficit. So, really, the end impact of these patients is just enormous, at least more than twice that of patients with slight to moderate strokes.

Just to give you a sense of how patients in general across the board do following intravenous thrombolysis for stroke--this is five trials of IV-tPA--this is the Modified Rankin Scale score at the bottom. Low scores are good, high scores are bad.

In general, the results are remarkably similar and about 40 percent of patients do pretty well; about 20 percent of patients do fair, and about 20 percent do poorly, and about 15-20 percent do very poorly and die. This is in contrast really to--if you look at the data from the PROACT II study, patients with very severe strokes, they just do miserably. And if you come in with an NIH Stroke Scale score of greater than 20, only about 10 percent of these patients will do well.

That patients with severe stroke do poorly was also illustrated in this study from Jose Suarez from Cleveland. This is a study of 54 patients treated intra-arterial thrombolysis. This is the initial NIH Stroke Scale score on this axis, the post-thrombolysis NIH Stroke Scale on this axis. A straight line means no improvement. If you end up below the line, you're better; if you're above the line, you're worse.

In this study, the initial NIH Stroke Scale score was the biggest predictor and the best predictor of who did well.

What you can see is that if you come in with a low score, a mild stroke, you're more likely to improve after treatment. If you come in with a high score, a very severe stroke, of greater than 15, the spread is much wider. It's kind of all over the map, and you're not necessarily likely to get better.

Also, if you look at this group here, no patient who improved got better than an 8, which many studies use as kind of the lower cut-off as what a minimal acceptable neurological deficit is. So we think that this group here is the best target for us to try to improve.

Clearly, there is a new for a new approach in patients with stroke, and particularly these patients with severe strokes who just don't do well. Even at the Cleveland Clinic, with the state-of-the-art kind of treatment that we have, the most aggressive therapy that we have, they just don't do well. And as Dr. Loftus briefly reviewed, there's overwhelming data to support the use of hypothermia in brain ischemia, and this has been used for 50 years in patients undergoing bypass surgery and neurovascular surgeries.

I won't go through all of the animal models, but I would like to focus on one important study. This is a study done out of University of Texas by Dr. Aronowski and colleagues, Dr. Grotta's group, and this is a rat model, an

MCA transient occlusion model, where they showed clearly that hypothermia significantly decreased the infarct volume and, perhaps more importantly, it was able to extent the narrow window of the duration of ischemia that the brain can withstand before permanent damage.

This is adapted from that study. Rats were cooled to 30 degrees five minutes before increasing durations of MCA occlusion, up to about 150 minutes. The mean infarct volume was 180 cubic millimeters, and the T50, which is the time it takes to reach half that maximum volume, was about 45 minutes.

In the hypothermia group, the mean infarct volume was 114 cubic millimeters, a 37 percent decrease, and the T50 was dramatically increased, a 50 percent increase, pushing to 70 minutes. And, in fact, hypothermia dramatically extended the time to 20 minutes before any noticeable sign of infarct was seen histologically. So hypothermia not only lowers the overall infarct but pushes the whole curve to the right.

One reason why these patients with severe strokes do poorly is that many of these patients suffer reperfusion injuries, so when the MCA recanalizes, it does so late; and then patients will get this biochemical cascade that can paradoxically antagonize the benefit of reperfusion. It's thought that this occurs from mainly the generation of free

radicals, and it's thought to occur mainly in three three-to six-hour vulnerable period and tends to diminish after 24 hours. Hypothermia in several other animal studies have shown reduction in the generation of free radicals, and so hypothermia in theory could prevent or attenuate this reperfusion injury.

Another reason, of course, why these patients do poorly is that they're at increased risk for hemorrhagic transformation. Overall, the rate of symptomatic hemorrhage in patients receiving intravenous tPA is about 5, 6, 7 percent. For these patients with severe stroke, it's at least double, 15, 18 percent. And that is, of course, the challenge of thermic therapy, is that delicate balance between the promise of benefit and the risk of hemorrhage.

Hypothermia in other animal models has been shown to tighten up the blood-brain barrier and potentially could evolve into a very strong adjunct to thrombolytic therapy.

I apologize about showing this slide. These are the kinds of slides that show up at all the stroke conferences with a billion arrows going everywhere. But this illustrates that ischemia is complicated, stroke is complicated. And I'd like to draw your attention to--I can't really with my pointer, but the main components of ischemia or the excitatory amino acid and calcium influx, which is in the top left, the generation of oxygen-free

radicals, and the blood-brain barrier and loss of microvascular integrity with an ensuing inflammatory response. Initially it was thought that hypothermia reduced the cerebral metabolic rate, but we now know that it's much more complicated how hypothermia works, but it probably works in a very diffuse way and suppresses all of these processes and results in less calcium, really the damage--less generation of oxygen-free radicals, and, again, maintaining the microvascular integrity.

So we think that hypothermia will evolve into a very powerful tool for the treatment of acute stroke, and it was based upon that premise that we developed this protocol and this pilot study which we called Cool AID. Cool AID was a pilot study we did at the Cleveland Clinic from last October to this September, focusing mainly on the feasibility, safety, and the preliminary effectiveness of hypothermia for severe acute stroke.

Briefly, patients were admitted--included if they had an MCA territory ischemic stroke. They had to have a severe stroke defined as a score of greater than 15. They had to get best therapy, so treatment with IV-tPA or intra-arterial thrombolysis or thrombectomy, and they had to have no significant improvement after treatment. So we didn't necessarily want to improve people who were--we didn't want to include people who were improving after their therapy.

We used surface cooling in this protocol. Patients were essentially wrapped in cooling blankets. We used whole-body ice and alcohol rubs. The target temperature was 32, and we monitored their temperature with a bladder probe.

This is the Cool AID team in action here, just to give you a sense of how labor-intensive this is. So we're rubbing the patients down with alcohol. These patients needed to be intubated, sedated, paralyzed, because they shiver. We followed their MCAs with TCDs.

So now I'm going to just turn this over to Dr. Krieger, who's going to go through the preliminary results of Cool AID.

DR. KRIEGER: Thanks, Michael. I also have no financial conflicts with this presentation.

As Mike already pointed out, the study was performed over a one-year period of time. During this time, 19 patients were screened for the study that mainly fulfilled the criteria of NIH's of 15 or more presenting within the time window that Michael presented, and 10 of those patients were undergoing hypothermia and 9 patients were screened for the study but were not included for several reasons, mainly because informed consent could not be obtained in time. And this just gives you kind of an idea of how they were.

The ages were pretty much the same, 68 on the normothermic side and 71 on the hypothermic side, and the stroke severity at presentation was about 20 in both groups.

Regarding the feasibility, I'm now pointing the attention to the 10 patients that underwent hypothermia. All patients were included within--induced with hypothermia within a mean of 6.2 hours, and it took about 3.6 hours to reach target temperature, which was 32 degrees. The duration of hypothermia varied according to the vascular status, but the mean cooling time at 32 degrees was 22 hours. But due to the differences in length and also the deliberate re-warming process, which we tried to keep at about 0.25 Centigrade per hour, we had a total duration of hypothermia of almost 50 hours.

This shows the difficulties that we have with steering our patients. It's like steering the Titanic. Once you have the momentum, you can't really steer it anymore. And so some of those patients dipped down to a chilly 28 degrees, and this shows you the wide variation around the target temperature that we have using the surface cooling technique.

This also illustrates that, again, 3.6 hours was the mean time to bring these patients down to hypothermia, and the lowest temperature reached was a mean of 30 degrees, and actually 90 percent of these patients overshoot. And

then the duration of time actually below temperature that was targeted at was 5.3 hours, which is 20 percent of the time that we had these patients in hypothermia.

Looking at the safety, without going through this complicated slide, the only trend of a difference was in bradycardia. Patients with hypothermia tended to have more bradycardia. And what we did is we kind of looked into no complication, mild complication, critical complication, and defined those on the basis of these indicators here. And the ones that I wanted to point out at the critical ones in the hypothermia group. And not that we think that they were actually related to the hypothermia process, we counted them, but they occurred in only four patients and two of those patients were very sick. This patient, for example, number 7, had a rupture of his aorta, Type 1, descending all the way down into the renal arteries and probably would have died anyway. And the other patient was a three-hour window tPA patients that developed an intracerebral hemorrhage that we observed in the 24-hour CT scan, and also died of the complications secondary to this phenomenon.

Basically what we want to show is that those marked in yellow, those complications occurred in patients that were steered within the limits of the therapy; that is, within a temperature window that was appreciated and also within a time window within 24 hours, because one of our

conclusions is that complications occur with longer periods of cooling, and so we would appreciate trials that are considering a time window of 24 hours to begin with if we're looking for the acute stroke indication.

In our clinical outcome, again, the natural history of patients with severe strokes is about 20 percent versus 80 percent, 20 percent good outcomes, 80 percent poor outcomes. Our normothermic nine patients kind of match that 10 percent and 90 percent as opposed to 50-50 in our hypothermia group.

And the radiological outcome, this is the normothermic group, this is the hypothermic group, and it is--as we already discussed earlier, it's a huge standard deviation, 129 cc's as opposed to 160 cc's, may be a trend.

And the conclusions are surface cooling is feasible for patients with severe acute ischemic strokes, but time to target temperature exceeds three hours, three hours being the thrombolytic time window.

Induced hypothermia is relatively safe, but complications occur with surface cooling methods, for example, intubation, sedation, paralysis, all the risk factors, at temperatures below 32 degrees and with prolonged cooling beyond 24 hours.

So better methods for temperature management are needed to allow faster induction and more precise control of

the cooling process. Induced hypothermia, according to our data, may improve outcome in patients with acute severe stroke, but additional clinical trials are needed to confirm this benefit.

And important considerations for clinical trials are: patient selection--I think we have to start working with moderate to severe strokes in order to be able to show benefit: time window--we should keep the time window as it is now, three hours, we should not try to extend it to 12 hours or 24 hours; we can do that later, but we have to show the proof of principle first and the best chance is getting them early; and the temperature depth is based on what the usual recommendations are, what usually is used in clinical trials; and also it has been shown that 32 degrees is probably the temperature that is--the deepest temperature that is well tolerated, to put it that way, and that's why we should start with that. And the endpoints, as we already discussed earlier, should be clinical or surrogate markers.

Thank you very much.

CHAIRPERSON CANADY: Thank you very much, Dr. Krieger.

Do we have anyone else who would like to speak?

[No response.]

CHAIRPERSON CANADY: If not, then we'll move to the industry speakers. I believe the first one is Dr. Chris

Ogilvy. I would remind you again to mention your affiliations and any financial interest you might have.

DR. OGILVY: Thank you. My name is Christopher Ogilvy. I'm Director of Cerebrovascular Surgery at Massachusetts General Hospital, associate professor at Harvard Medical School, and I'm speaking to you today as a medical consultant for Innercool Therapies, who paid for my trip here and $12 for lunch.

I'd like to begin to address the issue now of cooling in a mild way for neurosurgery, and I'll really focus my comments on neurosurgery and extend them at the end, open it up a little bit to some of the other possibilities you've been hearing about.

Now, the concept of using mild hypothermia neurosurgery has been around for a while, as the previous speakers have alluded to, and the concept is--the initial concept is to use mild hypothermia to minimize energy utilization, that is, glucose and oxygen utilization, during a phase of supply reduction, that is, energy reduction. And, amazingly, three degrees of hypothermia in the laboratory can reduce neural oxygen metabolism significantly, and that's been shown in a number of neural models. It's harder to show in whole brain situations.

Regardless of the exact mechanism of how hypothermia protects in a situation of stroke or ischemia,

the evidence from the laboratory is extremely compelling. And as Dr. Loftus alluded to, this has been used very extensively now or extensively by cerebrovascular neurosurgeons. The animal model, as I mentioned, is compelling and for neurosurgeons who work with blood vessels on a day-to-day basis and are essentially reproducing the animal models that are performed in laboratories, the utilization of this technique is similarly compelling and when alluding to temporary vessel occlusion during aneurysm surgery. This has become a fairly routine maneuver in probably 80 percent of neurosurgical operations in our institution and in others where aneurysms are clipped. The idea is to temporary occlude one or several of the vessels near an aneurysm to slacken the aneurysm during surgery and thereby safen the clipping and dissection of the aneurysm.

Intraoperative rupture of an intracranial aneurysm is associated with a tripling of the morbidity and mortality of that procedure.

Currently the techniques available for mild hypothermia include the blankets, ice packing, alcohol bathing, and cooling IV fluids that you've heard about. The problems also you've heard about, that is, slow temperature change, poor control of that temperature change, and sometimes difficult to administer.

In the operating room, in a very controlled

situation, and therefore, the idea of using an endovascular approach to control hypothermia is very attractive. Whether to extend it outside the operating room or not is a question for the future, I believe.

The advantages to this technique in the operating room is that you can get a rapid controlled temperature reduction. You can also precisely hit the target temperature and also rapidly and safely re-warm. The disadvantage is that it's invasive; however, it's an intravenous catheter which we use on a fairly regular basis. This is actually a photograph of the device of the device that we have been having some experience with in an early pilot trial of a multi-center nature where a catheter tip is cooled with counter-current exchange saline. The device is filled from a box that is outside the patient next to the operating bed, and the fluid is pumped through that catheter. It's fairly low cost. It's been proven to be reliable in our setting, and the idea is extremely simple in concept, that inserting this in the femoral vein into the interior vena cava during--as the operation is beginning, after the patient's induced with anesthesia, we can then use this to gently cool the patient down the three or four degrees that we require, and over a period, which I'll show you, the entire body cools to that temperature.

Similarly, the catheter can be used for the re-

warming phase of the procedure. And this just shows one of our colleagues inserting the catheter in a femoral vein, and then the X-ray confirmation of its location during the maneuver.

This graph shows two separate patients: one cooled with a cooling blanket and re-warmed, and one cooled with a catheter and re-warmed. And this has now been reproduced in a number of patients in the early pilot study, and as the operating surgeon, it has been impressive to me that when we're ready to do the aneurysm clipping in this phase, the temperature is at desired level and we don't have to wait or try to accelerate that.

Similarly, on the wake-up, when we're ready to wake the patient up at the conclusion of the procedure, the temperature is back where we want it in terms of a re-warming as opposed to waiting for the external device or external maneuvers to try to re-warm the patient.

In terms of outcomes to consider, one of the first, as you saw from the last presentation, is the ability to reach the desired temperature in the desired time, the ability to maintain that temperature, and the ability to safely re-warm the patient in the desired time.

In terms of safety parameters to look at and in the current study that are being looked at, first of all, of course, first and foremost, physical vascular injury to the

vessel being cannulated; secondly, liver function, cardiac function, and exclude patients, as others have mentioned, with blood dyscrasias or situations that would be exacerbated by mild hypothermia: cryoglobulinemia, serum cold agglutins, sickle cell disease, Raynaud's disease, Buerger's disease, and Thromboangiitis obliterans. These patients are currently excluded from the present study.

Now, the extension of mild hypothermia in other brain ischemia or injury situations is very attractive as well. Stroke has just been discussed, either prior to, during, or after a thrombolytic maneuver. For the neurosurgeon, the idea of using hypothermia for vasospasm is attractive, again, because in 20 to 30 percent of patients with subarachnoid hemorrhage, clinically significant vasospasm ensues--and this is a typo. It should be five to ten days after the hemorrhage. So during that window, patients can be watched with transcranial Doppler flow, and if vasospasm ensues, mild hypothermia could theoretically be added to the armamentarium already employed.

Also, head injury, as mentioned by Dr. Loftus, and fever reduction, which I believe the next speaker will address, in that hypothermia is extremely impressive in the laboratory in reducing stroke size, but avoiding hyperthermia may be more or possibly is more impressive in terms of reducing stroke size.

So considerations for this type of approach for hypothermia in other applications, it may also reduce ICP. There's some evidence of that nature in the literature. It can prevent the hyperthermia associated with fever. Downsides of this potential technique are the long indwell time of the catheter, although long-term use of venous catheters is commonly used in our ICU patients. This device may mask infection, any problem with any issue of mild hypothermia, and then we must address the issues raised by the last speaker of shivering in terms of thermoregulatory respond to cooling.

We're in the process is beginning to look at this type of technique to cool a patient and the gradients of cooling in terms of inducing or not inducing shivering. We don't have any answers there yet.

Thank you.

CHAIRPERSON CANADY: Thank you.

Our next speaker will be Dr. Diringer. Please identify yourself.

DR. DIRINGER: I'm Michael Diringer. I'm an associate professor of neurology, neurosurgery, and anesthesia at Washington University. I am a participant at the study center in a trial with Alsius looking at a device to control fever, and they have asked me to come and present some of my thoughts on design of trials for therapeutic

hypothermia, which we look at as entirely separate from fever control.

I think the first thing to emphasize is--I think as we sort of hear alluded to from several of the other speakers, we first have to define what the goal of the intervention is going to be, and really the empiric application in both head injury and in stroke has given us some ideas that are a little bit different from what we learned from the laboratory. And that is, in the laboratory we've seen most of the effects on neuroprotection, where we could potentially reduce the primary injury or prevent secondary injury.

The empiric data in patients that also we've seen is that this intervention may be very helpful in terms of limiting edema and helping control ICP. These two applications may require different degrees of hypothermia and may require different durations of therapy, so we have to be clear on what the goal of the treatment is. And as I mentioned, in large MCA stroke and head injury, ICP control may, in fact, be the more efficacious intervention, but yet that's going to really limit your applicability to a very small group of patients who have very severe disease.

So for the potential target populations, I think the point I want to make is we need to maybe enlarge the box a little bit. Currently, the way this is applied, patients

have to be intubated, so we are limited to severely affected patients. The questions that need to be posed and addressed are: Can hypothermia to maybe a lesser degree be utilized without the need for intubation and, thus, potentially reduce a large number of the complications, especially the pneumonia that is related not only to hypothermia but also to just being intubated?

In addition, we'll need to determine if these milder degrees of hypothermia both are improving neurological outcome and can be done more safely.

I think that the issue of control groups has come up repeatedly today, and I think in this area it's relatively clear. There has been no established efficacy in any application of hypothermia to date. There's a lot of preliminary data and suggestive data. But I think that in every application, randomized controlled trials are absolutely essential.

The issue that comes then is: How are the control groups and the experimental groups managed? And there is not only the intervention of the hypothermia, but the other ancillary interventions that come along with it, such as potentially intubation, sedation, use of paralytic agents. And I think that the studies have to address not only the intervention itself, but all the hardware that comes along with it so that it would not be appropriate, I think, to

take your control group and intubate, sedate, and paralyze them to make them more equivalent to the hypothermia group, because you want to look at the whole package. You want to take the patient treated as we do now and then compare the patients made hypothermic with all the other ancillary stuff that goes along with it.

In terms of ischemic stroke, as we've just heard, we're currently limited to large MCA strokes with swelling, and really the question, I think, that we need to address is: Is this technology and is this approach applicable to more moderate strokes? And can we achieve the hypothermia fast enough? The slides that we saw earlier this afternoon suggested that it prolongs the window, but I do want to point out that in that study hypothermia was induced prior to the insult. So we're still back to this three-hour window, and we still--but that relates to our goal. If our goal is neuroprotection, then we may need a much earlier onset of hypothermia. If the goal is reducing swelling and ICP control, the window conceivably could be longer.

In head injury, a randomized, NIH-funded, controlled trial has been completed. The results have not been officially announced. The word is that the trial was negative, and there's some important lessons from that trial. And the main important lesson is standardization of medical management. There are some--a lot of variation

across centers in that study in terms of how fluids and intravascular volume was managed. So I think it's extremely important in designing these trials that the medical management be nailed down and be very clear.

If you read the criteria for those trials, they were very clearly stated, but obviously in translating it into action, there was a lot of variation.

And, again, should we even repeat this trial? Should we use more mild head injuries that might potentially benefit? Those questions remain.

Cardiac arrest. I think that there is--obviously the window is the big question, and there's a couple of points along the window, the time from the arrest to the initiation of CPR, the time from the arrest until the restoration of circulation, and then a question of how long is the duration of cooling. Is this an area where we're dealing with reperfusion injury and maybe a 24- or 48-hour period of cooling might be necessary?

Subarachnoid hemorrhage. We've heard a lot about its use in the operating room during aneurysm repair and that a randomized trial is underway. Another potential application that hasn't been discussed as of yet is during the endovascular repair of aneurysms. External cooling has not been used in that setting because it's too cumbersome. Intravascular devices may be much easier to use, may cool

the patient more rapidly in this--using these endovascular techniques, there is also the risk of temporary or permanent vessel occlusion. So in this setting, this may also be a useful adjunct.

Also, as Dr. Ogilvy just discussed, potential use for reducing injury from vasospasm. Vasospasm is a stroke that's happening in front of our eyes. Here's a chance where we could potentially induce treatment prior to the onset of the stroke. The downside is that the duration of therapy is going to be quite long.

In terms of the dichotomous primary endpoints, we heard from the tPA trial we're looking at essentially normal or not. If you're looking at more severe populations, you may have to make that cut point between independent and dependent.

Temperature monitoring is an issue. There's a gradient between the brain and the core temperature. I think it would be unwise to require invasive brain monitoring of temperature in all studies unless there is another need for invasive monitoring, and that core temperature should be extrapolated.

I've alluded to the degree of hypothermia. Are more mild degrees of hypothermia efficacious? This is something we need to learn more about. And, of course, the duration of the hypothermia depends on the disease and the

goal. For ICP control after stroke, 48 hours may not be sufficient. Many of these patients go on to have rebound increases in ICP and die from that.

The longer duration of treatment may be limited by the complications, I think the most important of which we have to look for is pneumonia.

The rate of cooling can be much more rapid within intravascular devices, and this should enhance the neuroprotective effects. Re-warming we've learned is a big problem if it's done in an uncontrolled fashion, and potentially rates of maybe half a degree every six hours might prevent a lot of the rebound problems.

And, finally, I want to re-emphasize that we need to standardize other interventions. I've heard repeatedly today about best medical management. Well, we need to be very clear on how we define what that is and make sure that that's carried out as closely as possible between the control and experimental groups, and in a standard fashion across centers.

Thank you for your attention.

CHAIRPERSON CANADY: Thank you.

We have a couple quick minutes if anyone has any questions for any of the presenters.

[No response.]

CHAIRPERSON CANADY: Hearing none, I'd like to

move on to Dr. Grotta's presentation. Dr. Grotta is a consultant with the FDA's Peripheral and Central Nervous System Drug Advisory Committee, and he is going to give a presentation as one of the panelists.

x DR. GROTTA: Last year at the stroke meeting, we canvassed folks who gave various PowerPoint or slide presentations, and for the first year, I think there were more problems with slide presentations than PowerPoint presentations at last year's stroke meeting. So I finally decided to abandon Dr. Zivin's approach and go to the PowerPoint.

You all can see my talk backwards.

There we go.

Okay. Well, thank you. We've heard a lot already about the clinical trials that have been done. I'm going to review all these different areas and maybe give a few comments about how I think they relate to the questions that have been addressed to the panel.

As you've heard, there are several possible indications for hypothermia: global ischemic, or cardiac arrest, in the last ten years, in the English literature, I've found 611 citations of studies for global ischemia; and for focal ischemia, stroke, 654 citations; head trauma, 328 citations; also, we've heard for intra-operative cooling and possible other indications, such as intracerebral

hemorrhage. So, admittedly, what I'm going to say today is my own selection from among these large number of citations, and I did not go through each and every one of them.

There are many possible mechanisms for hypothermia. One important mechanism that's been shown in animal models is that excitatory neurotransmitter release is reduced, and perhaps there's less excito-toxicity. Blood-brain barrier integrity seems to be maintained under hypothermic conditions. Metabolic rate is reduced, and, importantly, what we've shown and others in the laboratory is that inflammatory response is reduced under hypothermic conditions. This may be particularly important in reperfusion and also after intracerebral hemorrhage.

Now, let me say a few things about preclinical studies, and in the next two slides, I want you to pay attention to the fact that the three most important lessons, I believe, about hypothermia from preclinical studies is that there is a very brief time window during which this therapy needs to be started to be effective. Number two, there seems to be an interaction with reperfusion, which I'll show you. And, thirdly, that there's an effect upon inflammation, as I've just alluded to.

This is an interesting study by Yanamoto and colleagues published last year in Stroke, and it's a little bit complicated but let me walk you through it. They used a

three-vessel occlusion model in a rat and then reperfused the brain and used four different--in addition to normal thermia throughout, they used four different experimental paradigms, whether the animal was made hypothermic during ischemia or also during reperfusion or just reperfusion or both. So, for instance, this group here had hypothermia during ischemia of two hours, but not during reperfusion, and there was no neuroprotection. This group had hypothermia to 33 degrees during the ischemic interval and then also during the first 21 hours of reperfusion, and that was associated with the greatest amount of neuroprotection.

This group had hypothermia during ischemia but only during the first three hours of reperfusion, and there was a significant effect, but less. And this group had only hypothermia during the reperfusion phase and none during ischemia, and, again, this did not quite reach statistical significance. So there seems to be the need to or at least greater benefit by having a hypothermic situation both during ischemia and during the reperfusion phase. This is a focal ischemia model.

In addition, hypothermia may amplify the effect of other therapies, and one of the things we need to think about, particularly as we talk a little bit more about mild hypothermia that has just been alluded to, is that maybe we can couple mild hypothermia with other neuroprotective

strategies to get an amplified effect. So, for instance, this is infarct volume in animals that have two-vessel occlusion without any therapy. This is the standard controls. Hypothermic animals had about a 50 percent reduction in infarct volume. Now, this was hypothermia just to 35 degrees, started 60 minutes after the onset of occlusion.

We have found in our lab that a combination of caffeine and ethanol actually, surprisingly, is also very neuroprotective, and we call it the Irish coffee therapy, and it causes about the same amount of neuroprotection as hypothermia. But, importantly, when you put all three of these together and make it iced Irish coffee, you get even greater effect.

So the point I want to make is that you can use modest hypothermia advantageously in combination with other therapies, perhaps to obtain clinical effect. That remains, of course, to be proven, but at least in the lab. And I think it's fair to say that among animal experimentalists, hypothermia is probably the most consistently effective neuroprotective approach that's been found. In virtually every lab that's tried to use hypothermia, they've seen that at least with focal ischemia that effect can be obtained.

Now, what are the phases of hypothermia--you've heard about this--clinically? There's an induction phase,

then a maintenance phase, and then a re-warming phase. The purpose of the induction phase is to reach the target quickly and, as Dr. Krieger pointed out, to avoid overshoot. Then you want to during the maintenance phase, of course, maintain temperature within a fairly narrow target. You want to maximize the physiology of the patient and avoid any of the complications physiologically that occur with hypothermia, and I'll come to that in a few minutes. And then there's the re-warming phase where you want to return gradually to a stable normothermic situation.

So let's go through these one by one now. I'm going to talk mainly about external cooling, which is the way this approach has been used mainly up to date.

During the induction phase, what's usually done is we put ice bags and other cooling pads or whatever immediately on the skin to give maximal surface contact. And you have as large a gradient as possible between the cooling blanket and the patient, so you circulate the iced water through the blanket as cold as you can possibly get it to try to get the patient down to the objective temperature. And you also can use iced gastric lavage and cooled inhaled gas as well to get the temperature down faster.

Then, very importantly, and actually not just during the maintenance phase but also during the induction phase, you need to paralyze the patient in order to get the

temperature below 35 degrees. And, in fact, even with the measures I've mentioned previously, you're really not going to get the temperature down unless you paralyze the patient to prevent shivering.

And then once you're at the maintenance phase, you maintain a small gradient between the external cooling blanket and the patient to keep the patient at a constant temperature level.

Now, what happens during the maintenance phase? There's vasoconstriction and you can get diuresis, resulting in a reduction of perfusion pressure. You can get bradycardia and arrhythmias. There's an intracellular shift of potassium, and coagulation factors have been pointed out earlier can be affected. Usually you see these things with prolonged hypothermia. With a day, 24 hours, as I'll show you in the cardiac arrest trials, these effects are pretty minimal.

It is important, since the patient is paralyzed, to pay attention to these other things, and I bring them up because they should be part of any clinical trial using hypothermia: careful skin care if the patient is paralyzed and not moving, frequent suctioning and pulmonary toilet; and when you're suctioning the patient, of course, particularly if you're a head trauma study, you need to have standardized methods, as Dr. Diringer pointed out, to